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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,323	SCHMITT ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-39* is/are pending in the application.

4a) Of the above claim(s) *36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/15/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 30-35 in Paper filed 5/10/04 is acknowledged.

2. Claims 36-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper filed 5/10/04.

3. Claims 30-35 are under examination.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 33 is indefinite for reciting "a double-fluorescence detection method" because the exact meaning of the phrase is not clear. Does the phrase mean detection with 2 antibodies each fluorescently labeled or one antibody with 2 labels or an antibody and a substrate wherein each is labeled. It is unclear what reagents are labeled and how many are needed for the method.

b. Claims 34 and 35 are indefinite for reciting "having a binding specificity equivalent to monoclonal antibody IIIF10" because it is not clear if the antibody has the

same affinity, avidity, binds the same antigen or some other "binding specificity" as the IIIF10 antibody.

c. Claims 30-35 are indefinite for reciting "reaction" in claim 1 because does the term mean the antibody reacts with the antigen/tumor cells as in a chemical reaction or does the term mean binding to the antigen/tumor cells?

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 34-35 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of IIIF10 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally

distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different VH chains (about 50% homologous) can combine with the same VK chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different VH sequences combine with different VK sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species IIIF10. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

8. Claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 recites a method for the diagnosis of tumors comprising contacting a sample with an antibody to residues 52-60 of uPAR. The claim is broadly drawn to any

uPAR from any source. The specification only teaches the human uPAR protein and an antibody directed against residues 52-60 of uPAR (see page 20). The specification does not teach a representative number of species for the genus claimed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is the recitation of a generic uPAR. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the human uPAR, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

9. Claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing tumors in a human comprising contacting the sample with an antibody directed against human uPAR of residues 52-60 and wherein detection of the antigen-antibody binding is indicative of the tumor and/or wherein the antibody comprises the CDRs of the IIIF10 antibody, does not reasonably provide enablement for a method of diagnosing tumors in a human comprising contacting the sample with a antibody directed against just any uPAR of residues 52-60 and wherein detection of the antigen-antibody binding is indicative of the

tumor and /or the antibody does not comprise the CDRs of the IIIF10 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of diagnosing tumors in any subject specifically a human with an antibody to residues 52-60 of any uPAR, specifically any species not human. Claim 35 is broadly drawn to any antibody that has the "binding specificity of the IIIF10 antibody but only has CDR3 of the VH and/or CDR3 of the VL.

The specification discloses a method of diagnosing tumors in human cells with an antibody to residues 52-60 of the human uPAR protein (see page 20, 21, 22). The specification teaches an antibody IIIF10 with a heavy and light chain of SEQ ID NO:2 and 4 (see page 23).

As evidenced from Li et al (US Patent 6,638,502 issued 10/03) the uPA binds to uPAR by its light chain and the area (amino acids 1-135) that this binding takes place is not conserved between mice and humans (see column 1, lines 55-61) and as such this

indicates that the mice and human uPAR are not conserved and as such one skill in the art would conclude that antibodies to 52-60 of human uPAR would not necessarily bind to the mice uPAR and could be used for diagnosis.

In addition claim 35 is broadly drawn to any antibody that has the "binding specificity" of the IIIF10 antibody and only has a CDR3VH and/or a CDR3VL of the IIIF10 antibody.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that

antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an IIIF10 antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dano et al (US Patent 5,519,120, issued 5/96) and further in view of Luther et al (American Journal of Pathology 150:1231-1244, 1997, IDS 10/15/01) and Heiss et al (Nature Medicine 1:1035-1039, 1995, IDS 10/15/01) and Terstappen (US Patent 5,234,816, issued 8/93, IDS 10/15/01).

The claims recite a method of diagnosing tumors in disseminated tumor cells in bone marrow comprising contacting the sample with an antibody to residues 52-60 of uPAR or the IIIF10 antibody in an ELISA to detect uPAR and the binding is determined by a double fluorescence detection method.

Dano et al teach antibodies to uPAR used for detection of the antigen in samples from a human in an ELISA (see column 13, lines 1-3, column 19) and the antibodies can be used for diagnosis of cancer (see column 18, lines 16-17) and the antibodies can be labeled with fluorescent agents (see column 18, lines 50-60, column 19, lines 10-17) and the preferred antibodies are those that inhibit the binding of uPAR to uPA which is in the N-terminal region of 1-87 of uPAR (see column 20, lines 35-51) and antibodies having this property are useful in a number of diagnostic utilities (see column 20, lines 24-26). Dano does not teach the IIIF10 antibody or the CDRs of the antibody or an antibody to specific residues of 52-60 of uPAR or the sample is bone marrow or a

double fluorescence method. These deficiencies are made up for in the teaching of Luther et al, Heiss et al and Terstappen.

Luther et al teach the IIIF10 antibody and the antibody binds to residues 52-60 of uPAR and this region is the region that is involved in binding of uPA to uPAR and antibodies to this region may facilitate the development of specific and efficient inhibitors of uPAR/uPA interaction (see page 1241) and the antibody was the best antibody in a flow cytometer analysis of biding to U937 cells (see abstract and page 1237). Luther also teach basic ELISA methods and fluorescence labels of antibodies for detection of cancer cells (see methods).

Heiss et al teach detection of uPAR in disseminated bone marrow cells using antibodies to uPAR and CK18 and a double staining method to determine the disease development (see abstract and page 1036, 1037-38).

Terstappen teach a method of diagnosing cancer by a method that uses two fluorescently labeled antibodies each binding to a different antigen to detect cancer in a bone marrow sample and each label has a different emission spectra to distinguish the antibodies (see column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of diagnosing tumor in a bone marrow sample in an ELISA or by a double-fluorescent method using an antibody to residues 52-60 of uPAR or the IIIF10 antibody in view of Dano, Luther, Heiss and Terstappen.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of diagnosing tumor in a bone marrow sample in an ELISA or by a double-fluorescent method using an antibody to residues 52-60 of uPAR or the IIIF10 antibody in view of Dano, Luther, Heiss and Terstappen because Danno et al teach methods of detection and diagnosis of tumors with an antibody that binds to the region in uPAR that uPA binds and using any such antibody and as taught by Luther et al this region is the same region that the IIIF10 antibody binds. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of diagnosing tumor in a bone marrow sample in an ELISA or by a double-fluorescent method using an antibody to residues 52-60 of uPAR or the IIIF10 antibody in view of Dano, Luther, Heiss and Terstappen labeled because Luther et al teach the IIIF10 antibody and this antibody resulted in the best antibody for detecting uPAR on cancer cells. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of diagnosing tumor in a bone marrow sample in an ELISA or by a double-fluorescent method using an antibody to residues 52-60 of uPAR or the IIIF10 antibody in view of Dano, Luther, Heiss and Terstappen labeled because Heiss et al teach a method of diagnosing tumors in bone marrow samples with an antibody to two antigens with one being uPAR and the combination of detection resulted in bettering the predictive outcome of individual disease development. Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method

of diagnosing tumor in a bone marrow sample in an ELISA or by a double-fluorescent method using an antibody to residues 52-60 of uPAR or the IIIF10 antibody in view of Dano, Luther, Heiss and Terstappen labeled because Terstappen teach a method of detecting tumors in bone marrow cells using two antibodies to two antigens and each was labeled with a different fluorochrome with a different emission spectra and one would substitute the labeling method of Heiss with that of Terstappen because the method of Terstappen would be far superior to the method of Heiss because in the Heiss method more than one antibody was used for detection of the primary antibody, i.e. secondary antibodies were used (see page 1238-9 of Heiss) and in the Terstappen method the primary antibody is labeled and used for detection, thus, simplifying the method. Thus, it would have been obvious to use an antibody to residues 52-60 in uPAR or the IIIF10 antibody to diagnose tumors in a bone marrow sample using a double fluorescent method or an ELISA because of the art known properties of antibodies directed to this region of uPAR and in view of Terstappen and Heiss et al who teach using two antigens to diagnose tumors in bone marrow sample.

Although claim 35 recites specific CDR sequences of the IIIF10 antibody, it would be obvious that the IIIF10 antibody of Luther has these sequences even though Luther et al is silent about the sequences.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ~~Christina Chan~~ JEFFREY SIEW, can be reached on (571) 272-~~0841~~ 0787.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER